Available online at www.sciencedirect.com

SciVerse ScienceDirect

Current Opinion in Neurobiology

Sick and tired: how molecular regulators of human sleep schedules and duration impact immune function

Philip A Kurien[1,4], SY Christin Chong[2,4], Louis J Ptáček[2,3] and Ying-Hui Fu[2]

Why do we need to sleep? What regulates when we sleep? And what dictates the number of hours we require? These are often viewed as three separate biological questions. Here, we propose they share molecular etiologies, whereby regulators of sleep schedules and sleep duration also govern the physiological purposes of sleep. To support our hypothesis, we review Mendelian human genetic variants sufficient to advance sleep-wake onset (*PER2*) and shorten sleep length (*DEC2*), and evaluate their emerging roles in immune responses that may rely on a sound night of slumber.

Addresses
[1] Department of Anesthesia, University of California San Francisco, San Francisco, CA 94143, United States
[2] Department of Neurology, University of California San Francisco, San Francisco, CA 94158, United States
[3] Howard Hughes Medical Institute, San Francisco, CA 94158, United States

Corresponding author: Fu, Ying-Hui (ying-hui.fu@ucsf.edu)

[4] These authors contributed equally to this work.

Current Opinion in Neurobiology 2013, **23**:873–879

This review comes from a themed issue on **Circadian rhythm and sleep**

Edited by **Clifford Saper** and **Amita Sehgal**

For a complete overview see the Issue and the Editorial

Available online 20th May 2013

0959-4388/$ – see front matter,

http://dx.doi.org/10.1016/j.conb.2013.04.014

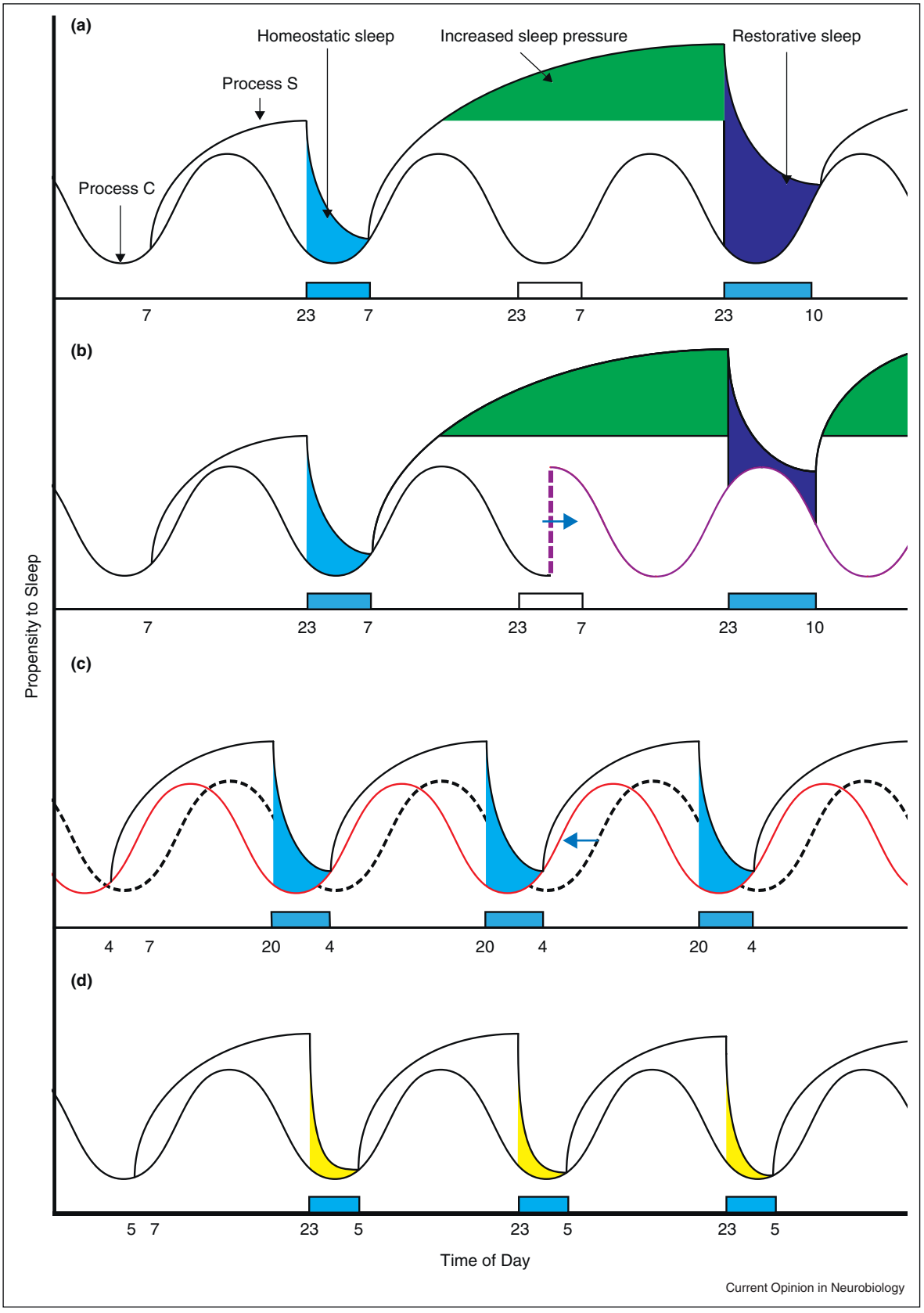
Introduction

Sleep is an innate behavior that is evidently circadian for modern humans because it is usually a daily, consolidated event with predictable timing. Quality of sleep is of utmost importance, but it remains difficult to define because its purpose is highly debated in light of many intriguing possibilities [1,2]. Besides restorative biological processes, optimal sleep in conventional society also takes into account its timing (i.e. sleep schedules relative to the time of day, also known as Process C due to its association with circadian rhythmicity) and its duration (i.e. the number of hours that yield satiety, also known as sleep homeostasis or Process S) (Figure 1a) [3]. Sleep disorders such as insomnia or sleep deprivation distort the relationship between Processes C and S and affect both (Figure 1b). Other variations in sleep patterns include those that specifically affect Process C such as advanced sleep phase (where affected individuals feel sleepy in the late afternoon and wake up before sunrise, though the total amount of sleep remains conventional) (Figure 1c), and those that perturb only Process S such as natural short sleep (Figure 1d) [4]. Therefore, understanding the biological underpinnings of Processes C and S may lead to targeted treatment for sleep disorders.

It is a common belief that there are separate molecular pathways for Processes C and S, and there may be coordinated mechanisms between them that together ensure 'optimal' sleep quality. Therefore, the molecular basis of the two-process model is sometimes simplified as a Venn diagram with two partially intersecting circles (Figure 2a). Process C is better understood compared to Process S because it is associated with the 'molecular core clock,' which defines a series of mechanisms that allow a cell to maintain circadian rhythmicity. The most defined aspects of the molecular core clock are a series of transcription-translation negative feedback loops that take approximately 24 hours to complete [5,6]. But despite a remarkable correlation between cellular and behavioral circadian periods (the time it takes to complete one cycle) [7], it is not clear how the molecular core clock regulates timing of sleep onset and offset. The molecular basis of Process S is even more nebulous because it is challenging to define and assay sleep homeostasis *in vitro*. Therefore, identifying molecular components sufficient to alter sleep timing and duration is of high research interest.

Through the identification of Mendelian human sleep traits, genetic mutations that result in advanced sleep phase (*PER2*) and shortened sleep duration (*DEC2*) were found [8–10]. With regard to the two-process model, *PER2* appear to participate in Process C and *DEC2* in Process S. Interestingly, emerging evidence suggests an intimate relationship between Processes C and S, and clinical outcomes related to immune responses. Is it possible that instead of directly sharing molecular mechanisms, Processes C and S may instead coordinate through participating in physiological reasons for sleep such as immune function? Here we posit that *PER2* and *DEC2* may function as regulators of sleep timing and duration respectively, yet both simultaneously impact the immune system via separate mechanisms (Figure 2b). Together, this hypothesis explains the observed correlation between sleep and immune responses, and also supports an alternative view of the two-process model. Finally, we discuss the challenges of untangling the molecular basis of sleep regulation (how much sleep

Figure 1


(a)
Homeostatic sleep
Increased sleep pressure
Restorative sleep
Process S
Process C
7
23
7
23
7
23
10
(b)
7
23
7
23
7
23
10
(c)
4
7
20
4
20
4
20
4
(d)
5
7
23
5
23
5
23
5
Propensity to Sleep
Time of Day
Current Opinion in Neurobiology